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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>IB/G-32677A/BCK | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/EP 03/10289 | International filing date *(day/month/year)*<br>16.09.2003 | Priority date *(day/month/year)*<br>17.09.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>C07K14/37 | | |
| Applicant<br>SANDOZ AG et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 29.03.2004 | 04.11.2004 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Turri, M<br>Telephone No. +49 89 2399-7712 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/10289

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-19 as originally filed

**Claims, Numbers**

1-22 as originally filed

**Drawings, Figures**

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-22 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-22 |
| Industrial applicability (IA) | Yes: | Claims | 1-22 |
| | No: | Claims | |

2. Citations and explanations

   **see separate sheet**

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

   D1: MARATHE S ET AL: "DUPLICATION-INDUCED MUTATION OF A NEW NEUROSPORA GENE REQUIRED FOR ACETATE UTILIZATION PROPERTIES OF THE MUTANT AND PREDICTED AMINO ACID SEQUENCE OF THE PROTEIN PRODUCT" MOLECULAR AND CELLULAR BIOLOGY, vol. 10, no. 6, 1990, pages 2638-2644, XP009026209 ISSN: 0270-730

   D2: CONNERTON I F ET AL: "AN ACETATE-SENSITIVE MUTANT OF NEUROSPORA-CRASSA DEFICIENT IN ACETYL-COA HYDROLASE" JOURNAL OF GENERAL MICROBIOLOGY, vol. 138, no. 9, 1992, pages 1797-1800, XP001179486 ISSN: 0022-1287

   D6: ULLAN R V ET AL: "A novel epimerization system in fungal secondary metabolism involved in the conversion of isopenicillin N into penicillin N in Acremonium chrysogenum" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 277, no. 48, 29 November 2002 (2002-11-29), pages 46216-46225, XP002261579 ISSN: 0021-9258

2. The problem to be solved by the present application resides in the provision of a gene in *Acremonium chrysogenum* which, when overexpressed, results in a augmented production of cephalosporin C.

3. The applicant has cloned a gene from *Acremonium chrysogenum* encoding a protein presenting 77,3% identity with Acetyl-CoA hydrolase from *Neurospora crassa* disclosed in documents D1 and D2. This gene doesn't seem to have any obvious relationship with the biosynthetic pathway of cephalosporin.

4. In Examples 2 and 3, the plasmid containing the gene is transformed in *A. chrysogenum*, and the transformants are tested for cephalosporin production. In Example 3 (page 13,

last statement of the first paragraph), it is said that "*it is possible to identify* in this way strains [...] which have reproducibly a distinctly higher cephalosporin productivity". The example itself, however, *does not show* that such transformants do actually produce more cephalosporin, nor - as said in point 3. above ,- this effect would seem to be obvious.

5. In the other examples of the application, the plasmid containing said gene is extended by other cephalosporin biosynthesis genes: in Example 4, by the cefD1 and cefD2 genes; in Example 5, by the pcbAB and pcbC genes; in Example 6, by the cefEF and cefG.

6. An effect on the production of cephalosporin following transformation with one of the above plasmids is *only shown* in Example 8, where the transformation with Plasmid 2, containing the identified gene plus the two cephalosporin biosynthesis genes cefD1 and cefD2 results in a 10% increased production of cephalosporin.

7. These effect can hardly be considered as surprising, since the two genes are known to be part of the cephalosporin biosynthetic pathway, and also that their concerted action is required (see Document D6, abstract).

8. Additionally, the application does not show that the above effect is due to the simultaneous expression of the cloned *and* cefD1 and cefD2 genes (resulting either in a additional or in a synergistic effect). Indeed, no experiments do show that when the cefD1 and cefD2 genes are expressed alone - i.e., together, but without the cloned gene - the same increase of 10% cannot be achieved.

9. The cloned gene, therefore, does not solve the above problem. Consequently, the present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of claims 1-22 does not involve an inventive step in the sense of **Article 33(3) PCT**.